

# Body weight changes and incidence of cachexia after stroke

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## Abstract

**Background** Body weight loss is a frequent complication after stroke, and its adverse effect on clinical outcome has been shown in several clinical trials. The purpose of this prospective longitudinal single-centre observational study was to investigate dynamical changes of body composition and body weight after ischemic stroke and an association with functional outcome.

**Methods** Sixty-seven consecutive patients (age  $69 \pm 11$  years, body mass index  $27.0 \pm 4.1$  kg/m<sup>2</sup>, 42% female patient, mean  $\pm$  SD) with acute ischemic stroke with mild to moderate neurological deficit (National Institute of Health Stroke Scale median 4, ranged 0–12) were analysed in the acute phase ( $4 \pm 2$  days) and at 12 months ( $389 \pm 26$  days) follow-up. Body composition was examined by dual energy X-ray absorptiometry. Cachexia was defined according to the consensus definition by body weight loss  $\geq 5\%$  within 1 year and additional clinical signs. Lean tissue wasting was considered if a ratio of upper and lower limbs lean mass sum to squared height (kg/m<sup>2</sup>) was  $\leq 5.45$  kg/m<sup>2</sup> for female patient and  $\leq 7.25$  kg/m<sup>2</sup> for male patient.

**Results** According to the body weight changes after 12 months, 42 (63%) patients had weight gain or stable weight, 11 (16%) patients had moderate weight loss, and 14 (21%) patients became cachectic. A relative decline of 19% of fat tissue and 6.5% of lean tissue was observed in cachectic patients, while no changes of lean tissue were observed in non-cachectic patients after 12 months. The modified Rankin Scale was 48% higher ( $2.1 \pm 1.6$ ,  $P < 0.05$ ), Barthel Index was 22% lower ( $71 \pm 39$ ,  $P < 0.01$ ), and handgrip strength was 34% lower ( $21.9 \pm 13.0$ ,  $P < 0.05$ ) in cachectic compared to non-cachectic patients after 12 months. The low physical performance if defined by Barthel Index  $< 60$  points was linked to the lean tissue wasting (OR 44.8,  $P < 0.01$ ), presence of cachexia (OR 20.8,  $P < 0.01$ ), and low body mass index  $< 25$  kg/m<sup>2</sup> (OR 11.5,  $P < 0.05$ ). After adjustment for co-founders, lean tissue wasting remained independently associated with the low physical performance at 12 months follow-up (OR 137.9,  $P < 0.05$ ).

**Conclusions** In this cohort study, every fifth patient with ischemic stroke fulfilled the criteria of cachexia within 12 months after index event. The incidence of cachexia was 21%. Cachectic patients showed the lowest functional and physical capacity.

**Keywords** Body weight; Body composition; DXA; Stroke; Cachexia

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## Introduction

Stroke is a leading medical, socio-economic and health care problem worldwide. Increasing global life expectancy and a reduction of the acute post-stroke mortality rate contribute to the rising costs in stroke care.<sup>1–3</sup> About two thirds of the patients remain disabled after stroke.<sup>4,5</sup> The course of post-stroke recovery depends on the initial stroke severity and stroke-related complications including inflammation, infection, metabolic dysfunction, and degree of disability. Several clinical trials have shown an important role of body weight and nutritional status at stroke onset for the functional outcome and mortality after stroke<sup>6–8</sup> and an association between the body weight and mortality in experimental stroke.<sup>9</sup>

Body weight loss after stroke is a common observation in acute and chronic stroke.<sup>6</sup> However, detailed information on body composition changes after stroke are scarce.<sup>10,11</sup> Standardized assessment of body composition is feasible using dual-energy X-ray absorptiometry (DXA), bioelectrical impedance, or computer tomography.<sup>12–14</sup> Tissue wasting or cachexia is a complex metabolic syndrome of multifactorial origin<sup>15</sup> that has been most frequently shown in association with several chronic diseases including chronic heart failure, chronic obstructive pulmonary disease, kidney disease, or cancer.<sup>16–19</sup> The reported prevalence of cachexia ranges between 5% and 80% depending on disease and disease severity and has been linked to poor outcome.<sup>20,21</sup> However, the incidence of cachexia has not been studied in detail in patients with ischemic stroke.

The aim of this prospective observational study was to analyse changes of body weight and body composition and to investigate the functional outcome in cachectic and non-cachectic patients with stroke.

## Methods

### *Ethical conduct and study population*

The investigator-initiated single-centre longitudinal prospective observational body size in stroke study<sup>22</sup> (German registry for clinical trials number DRKS00000514) was approved by the Ethic Committee of Charité-Universitätsmedizin Berlin, Germany (EA2/008/09), and written informed consent was obtained from all patients.

We studied 67 patients with acute ischemic stroke within the territory of the middle cerebral artery. The patients with mild to moderate neurological deficit [defined by the National Institute of Health Stroke Scale (NIHSS)  $\leq 12$  points] were consecutively enrolled within 48 h after stroke onset while being admitted to a stroke unit (Department of Neurology, Charité-Universitätsmedizin Berlin, Campus

Virchow-Klinikum, Berlin, Germany) from June 2009 to November 2012. Following the discharge from the stroke unit, 34 patients were admitted to post-stroke rehabilitation. These patients underwent adjusted early post-stroke rehabilitation programs in specialized rehabilitative clinics according to national standards for rehabilitation procedures after stroke.

Study related examinations included assessments of body composition, physical and functional capacity, muscle strength, and nutritional status and were completed in hospital at baseline ( $4 \pm 2$  days after the index event) and at 12 months follow-up ( $389 \pm 26$  days after stroke onset) visit. According to the changes of the body weight after 12 months, patients were retrospectively grouped into (i) weight gain/stable weight, (ii) moderate weight loss ( $<5\%$  of body weight), and (iii) cachectic subgroups. Cachexia was defined by weight loss  $\geq 5\%$  of the original weight over a period of 12 months and at least three clinical criteria according to the current consensus definition.<sup>15</sup>

### *Assessment of functional outcome and muscle strength after stroke*

Functional capacity and degree of disability were assessed by the Barthel Index (BI) and by the modified Rankin Scale (mRS).<sup>23</sup> The BI contains 10 basic activities of the daily living related to self-care and mobility with scores of '0' to '100', where the lower scores indicate greater dependency. Low functional status was defined by the BI  $<60$  points.

The mRS measures physical independency by assessment of the body function, activity, and participation in daily tasks on the scale ranging from '0' (no symptoms) to '6' (death). Isometric muscle strength of the hand was assessed by the handgrip strength test using a handgrip dynamometer (Saehan Corporation, Korea). The highest of three handgrip measurements of the non-paretic hand was used for analyses.

Maximal isometric muscle strength of the quadriceps muscle (expressed in Newton, N) was measured as described previously.<sup>24</sup> Briefly, the freely hanging legs of the sitting patients were connected at the ankle with a pressure transducer (Multitrace 2, Lectromed, Jersey, Channel Islands), and maximal isometric strength was assessed from the best of three contractions on each leg, with a resting period of at least 60 s in between.

### *Body composition*

Body mass index (BMI) was calculated as a ratio of body weight and squared height ( $\text{kg}/\text{m}^2$ ). For detailed body composition assessment, dual-energy DXA was performed using LunarProdigy densitometer (GE Healthcare, Chalfont St. Giles, UK). Total body scans were analysed to obtain total and regional (upper and lower limbs, and trunk) measurements

of the fat and lean tissue. The sum of the lean or fat mass of the upper and lower limbs was termed as an appendicular muscle mass (ALM) or appendicular fat mass. The fat-free mass index (FFMI) was calculated as a ratio of ALM and squared height ( $\text{kg}/\text{m}^2$ ). Lean tissue wasting was defined by low FFMI (for female patient  $\leq 5.45 \text{ kg}/\text{m}^2$  and for male patient  $\leq 7.25 \text{ kg}/\text{m}^2$ ).

Appetite was assessed according to the visual analogue scale ranging from '0' (no appetite) to '10' (very good appetite).<sup>25</sup> In addition, nutritional status was assessed by Mini Nutritional Assessment at 12 months as follows: patients were undernourished, if they achieved 16 points or less, at risk for malnutrition if they achieved 17–23.5 points, or had a normal nutritional status if they achieved  $\geq 24$  points.<sup>26</sup>

None of the patients included in our study had dysphagia on a clinical relevant level (preventing oral feeding), and none was fed enterally or parenterally.

### Blood sampling

Venous blood samples were obtained in all patients after 12 h of overnight fasting. Standard biochemical parameters were assessed by routine laboratory measurement. Systemic inflammation was present if C-reactive protein (CRP) plasma level was over  $6.1 \text{ mg}/\text{dL}$ , as defined previously.<sup>27</sup>

## Statistical analysis

All data were presented as means  $\pm$  standard deviation, median (interquartile range), or percentage as appropriate. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Non-normally distributed data were log transformed to achieve a normal distribution where indicated. Statistical comparisons were made using paired or unpaired Student's *t*-tests as appropriate, analysis of variance followed by Fisher's *post hoc* test, Mann–Whitney, or Kruskal–Wallis test. Chi-squared test was used to assess categorical distribution between the groups. Pearson's simple regression and logistic regression were used as appropriate. A value of  $P < 0.05$  was considered statistically significant. Statistical analyses were performed with the StatView 5.0 software package (SAS Institute Inc, Cary, NC) and the software GraphPad Prism 6.0.

## Results

Baseline clinical characteristics of the patients and retrospective study subgroups are presented in *Table 1*. Twelve months after stroke, 42 (63%) patients had stable weight or weight gain, 11 (16%) of all patients were found

with moderate weight loss, and 14 (21%) patients became cachectic (*Figure 1*). There were no significant differences regarding the BMI, the side of stroke-related brain damage, thrombolytic therapy, frequency of paresis, or admission to post-stroke rehabilitation at baseline between all subgroups. Patients who became cachectic 12 months after stroke were significantly older ( $P < 0.05$ ), had more frequently advanced neurological deficit with NIHSS  $\geq 5$  (64%,  $P < 0.05$ ), had higher degree of dependence by mRS ( $P < 0.01$ ) and BI ( $P < 0.05$ ), and had the lowest albumin and the highest CRP serum levels ( $P < 0.001$  and  $P < 0.01$ , respectively) at baseline compared to other subgroups (*Table 1*).

According to univariate regression analysis, baseline parameters including age, neurological deficit as indicated by a NIHSS  $\geq 5$  points, functional dependency as indicated by mRS and BI, albumin and log-transformed CRP serum levels, systemic inflammation as defined by CRP serum levels  $> 6.1 \text{ mg}/\text{dL}$ , self-reported appetite, and handgrip strength were associated with cachexia onset (*Table 2*). After adjustment for age, sex and BMI, systemic inflammation, and CRP serum levels were independently associated with cachexia development (*Table 2*).

### Body composition

At baseline, no differences in body composition were observed among study subgroups (*Table 3*). While in the stable weight/weight gain group no loss of lean mass after 12 months was observed, patients with weight loss showed a reduction in lean mass (*Table 3*). Thus, in patients who became cachectic, a significant reduction of ALM by 6.5% ( $P < 0.05$ ) was observed (*Table 3*). The frequency of the lean tissue wasting as defined by FFMI  $\leq 5.45 \text{ kg}/\text{m}^2$  for female patient and FFMI  $\leq 7.25 \text{ kg}/\text{m}^2$  for male patient in the cachectic subgroup was 43% after 12 months ( $P < 0.001$ ) vs. baseline. In addition, appendicular fat mass 12 months after stroke was also the lowest in cachectic patients ( $P < 0.05$ ).

In the stable weight/weight gain group and the moderate weight loss group, no significant reduction of lean tissue according to the FFMI was observed (*Table 3*). Lean tissue wasting showed no relation to paresis in the studied patients, (OR 1.1, 95% CI [0.12–10.6],  $P = 0.9$ ).

### Functional outcome at 12 months follow-up

Clinical characteristics of the patient subgroups at 12 months follow-up are shown in *Table S1*. Twelve months after stroke an improvement of functional capacity compared to baseline was found in most patients with stroke (*Figure 2A* and *2B*). This improvement applied to patients with and without cachexia. Nonetheless, cachectic patients

**Table 1.** Clinical characteristics of study cohort at baseline

Parameter	Study group	Weight gain/stable weight	Moderate weight loss	Cachexia	P-value
	n = 67	n = 42	n = 11	n = 14	
Age, years	69 ± 11	66 ± 11	70 ± 10	75 ± 9	0.03
Male sex; % (n)	58 (39)	60 (25)	82 (9)	36 (5)	0.07
Body mass index, kg/m <sup>2</sup>	27.0 ± 4.1	26.5 ± 3.7	28.7 ± 5.1	26.4 ± 4.8	0.3
Body mass index <25 kg/m <sup>2</sup> ; % (n)	30 (20)	31 (13)	18 (2)	36 (5)	0.6
Systolic RR, mmHg	138 ± 24	136 ± 21	150 ± 27	138 ± 30	0.2
Diastolic RR, mmHg	77 ± 13	77 ± 12	82 ± 14	73 ± 14	0.1
Mean RR, mmHg	97 ± 15	96 ± 14	105 ± 17	94 ± 14	0.2
Stroke severity					
Thrombolysis with rt-PA; % (n)	31 (21)	29 (12)	27 (3)	43 (6)	0.6
Right hemispheric stroke; % (n)	66 (42)	60 (25)	73 (8)	75 (9)	0.7
Paresis; % (n)	84 (56)	86 (36)	82 (9)	79 (11)	0.8
Post-stroke rehabilitation; % (n)	51 (34)	52 (22)	46 (5)	50 (7)	0.9
NIHSS score	4.5 ± 3.2	4.3 ± 3.2	3.5 ± 2.7	5.8 ± 3.0	0.2
NIHSS score 5–12; % (n)	37 (25)	33 (14)	18 (2)	64 (9)	0.02
Modified Rankin Scale score	2.0 ± 1.3	1.8 ± 1.1	1.6 ± 1.0	3.0 ± 1.4	0.003
Modified Rankin Scale score 4–5; % (n)	18 (12)	12 (5)	9 (1)	43 (6)	0.02
Barthel Index score	78 ± 29	82 ± 26	88 ± 20	60 ± 38	0.03
Barthel Index score < 60	27 (18)	21 (9)	12 (2)	50 (7)	0.09
Comorbidities					
Diabetes mellitus; % (n)	27 (18)	17 (7)	55 (6)	36 (5)	0.03
Hypertension; % (n)	84 (56)	83 (35)	82 (9)	86 (12)	0.9
Dyslipidemia; % (n)	59 (39)	55 (23)	82 (9)	50 (7)	0.2
Biochemistry					
Haemoglobin, g/dL	14 ± 2.0	14.0 ± 1.9	14.5 ± 1.1	13.6 ± 2.7	0.5
Albumin, g/L	36.8 ± 5.6	37.4 ± 5.9	39.1 ± 3.3	32.2 ± 5.9	0.001
Glucose, mg/dL	115 ± 44	114 ± 46	136 ± 45	100 ± 24	0.2
HbA1c, %	6.2 ± 1.4	6.0 ± 1.2	6.7 ± 1.5	6.4 ± 1.8	0.2
Sodium, mmol/L	140 ± 4	141 ± 3	139 ± 6	141 ± 4	0.6
Potassium, mmol/L	4.1 ± 0.4	4.1 ± 0.3	4.0 ± 0.5	4.0 ± 0.5	0.9
Triglyceride, mg/dL	151 ± 71	154 ± 75	142 ± 43	156 ± 81	0.7
Cholesterol, mg/dL	196 ± 44	198 ± 45	176 ± 49	203 ± 38	0.5
Low density lipoprotein, mg/dL	114 ± 42	113 ± 45	114 ± 37	128 ± 26	0.3
High density lipoprotein, mg/dL	51 ± 15	54 ± 17	50 ± 11	46 ± 14	0.2
Creatinine, mg/dL	1.0 ± 0.5	1.1 ± 0.5	1.1 ± 0.3	0.9 ± 0.2	0.8
C-reactive protein, mg/L	3.8 [1.8–6.3]	3.4 [1.7–6.6]	1.7 [1.0–4.8]	8.8 [4.6–22.4]	0.002
Uric acid, mg/dL	5.7 ± 1.4	5.6 ± 1.5	5.7 ± 1.3	5.9 ± 1.2	0.9

NIHSS, National Institute of Health Stroke Scale.

remained with the more severe disability as shown by the higher mRS score ( $2.1 \pm 1.6$ ,  $P < 0.01$ ) and lower BI score ( $71 \pm 39$ ,  $P < 0.01$ ) compared to other study subgroups (Figure 2A and 2B). Better functional capacity according to the BI was associated with weight gain ( $R = 0.25$ ,  $P < 0.05$ ) in all patients with stroke (Figure 2C).

Cachectic patients showed the lowest muscle strength as assessed by handgrip strength test and quadriceps strength test (Figure 3A and 3B). An association between the FFMI and handgrip strength was observed in non-cachectic ( $R = 0.54$ ,  $P < 0.0001$ ) and in cachectic ( $R = 0.71$ ,  $P < 0.01$ ) patients at 12 months follow-up (Figure 3C).

Univariate logistic regression analysis showed an association of low functional status as defined by BI score <60 points with the lean tissue wasting, presence of cachexia, BMI, body weight loss, nutritional status, low albumin, and high CRP serum levels (Table 4). After adjustment for covariates included age and sex, lean tissue wasting and FFMI remained independently associated with low functional status.

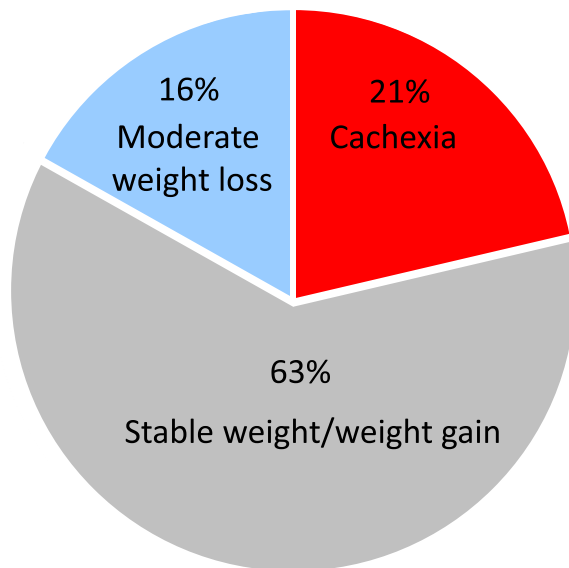
### Nutritional status at 12 months follow-up

Significant improvement of the appetite according to the visual appetite scale was observed in patients with weight gain/stable weight but not in those with any degree of weight loss (Figure 4A). Cachectic patients were found with the lowest appetite and nutritional status (Figure 4A and 4B). A direct association between the weight gain and appetite was observed ( $R = 0.4$ ,  $P < 0.002$ , Figure 4C).

### Systemic inflammation

At 12 months follow-up, inflammatory activity was still ongoing in cachectic patients [median CRP 7.6 (interquartile range 2.6–15.2) mg/dL,  $P < 0.01$ ] compared to the other subgroups (Table S1). Lean tissue wasting, nutritional status, self-reported appetite, mRS, BI, and handgrip strength were associated with systemic inflammation (Table 5).

**Figure 1** Body weight changes at 12 months follow-up in the study population. Incidence of cachexia.



## Discussion

Our study demonstrates an incidence of cachexia of 21% within 1 year after stroke. Physical and functional clinical status at 12 months follow-up was lower in cachectic patients compared to non-cachectic patients with stroke. We also identified clinical parameters predictive for development of cachexia after stroke.

## Tissue wasting

Using DXA analyses, we showed that patients with cachexia, in contrast to patients without cachexia, lost fat mass and lean tissue. Loss of lean mass in paretic patients with stroke, having sedentary lifestyle, is a common observation.<sup>28–30</sup> However, we observed a lean tissue depletion in cachectic patients regardless of the paresis. Previously, a stroke-related systemic lean tissue wasting due to catabolic activation was reported in a mouse model of middle cerebral artery occlusion.<sup>9</sup> The extent of the brain damage in mice correlated with apoptotic and proteolytic activity in skeletal muscle in both legs.<sup>9</sup> In line with this experimental data, we observed an association between the stroke severity and the presence of cachexia.

Certainly, lean tissue decline is an age-dependent phenomenon, with the prevalence ranging between 8% and 60% in healthy elders.<sup>31–35</sup> Previous study showed a prevalence of sarcopenia of 7% in chronic stroke survivors within 3 years after ischemic or haemorrhagic stroke.<sup>10</sup> In the present cohort, the prevalence of the lean tissue depletion at the time of the index stroke was within the generally observed age-dependent range. However, an increase from 6% to 13% in the prevalence of lean tissue depletion within 12 months with the highest proportion among cachectic patients (43%) might be linked to stroke-related metabolic imbalance.<sup>36</sup>

## Systemic inflammation

An association between cachexia and inflammatory state in patients with chronic heart failure or chronic obstructive

**Table 2.** Baseline parameters associated with cachexia onset after stroke

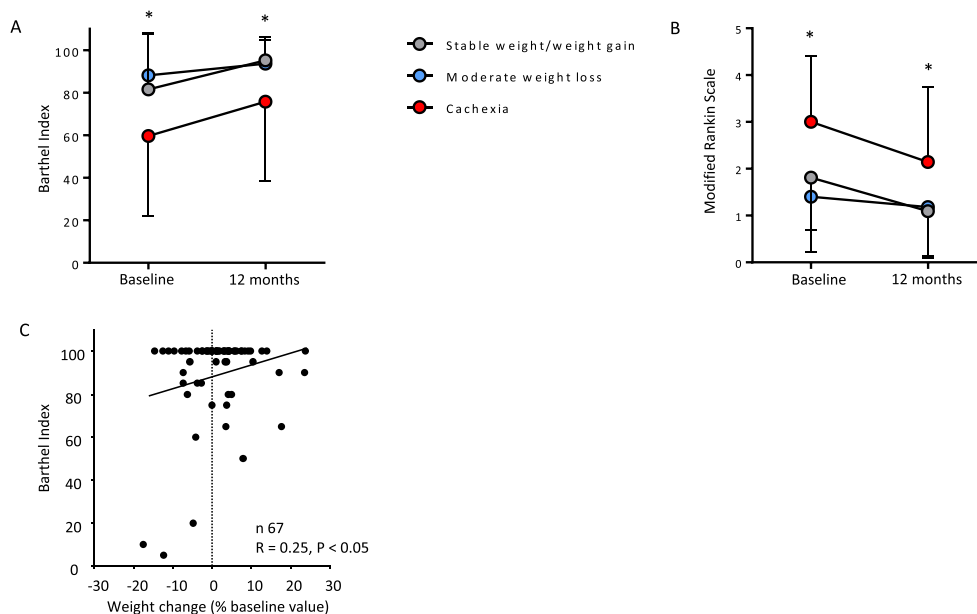
Parameter	OR	95% CI	P-value
Presence of systemic inflammation	8.54	[2.27–32.17]	0.002
C-reactive protein, log[mg/L]	7.93	[1.99–31.60]	0.003
NIHSS 5–12 points	4.16	[1.20–14.39]	0.02
Barthel Index <60 points	3.80	[1.10–13.20]	0.03
Modified Rankin Scale, point	2.19	[1.32–3.65]	0.003
Age, year	1.08	[1.01–1.15]	0.02
Barthel Index, 10 points	0.78	[0.64–0.95]	0.02
Handgrip strength, kg	0.91	[0.85–0.98]	<0.01
Albumin, g/dL	0.79	[0.68–0.92]	0.002
Appetite, point VAS	0.51	[0.34–0.77]	0.002
Appendicular lean mass, kg	0.83	[0.70–0.99]	0.03
Lean mass upper limbs, kg	0.58	[0.34–0.99]	<0.05
Lean mass lower limbs, kg	0.76	[0.60–0.96]	0.02
Multivariable logistic model adjusted for age, sex, and BMI			
I. Systemic inflammation	9.66	[1.96–47.63]	0.005
II. C-reactive protein, log[mg/L]	6.67	[1.34–33.12]	0.02

NIHSS, National Institute of Health Stroke Scale; VAS, visual analogue scale.

**Table 3.** Body composition in patient subgroups

Parameter	Weight gain/stable weight		Moderate weight loss		Cachexia	
	Baseline	12 months	Baseline	12 months	Baseline	12 months
Body mass index, kg/m <sup>2</sup>	26.7 ± 3.5	28.2 ± 4.9***	28.7 ± 5.1	27.9 ± 4.9**	26.4 ± 4.8	24.2 ± 4.5**†††
FFMI, kg/m <sup>2</sup> , female patient	6.4 ± 0.8	6.6 ± 0.7	6.5 ± 0.04	6.6 ± 0.1	6.1 ± 0.8	6.0 ± 1.3 <sup>†</sup>
FFMI, kg/m <sup>2</sup> , male patient	8.3 ± 0.7	8.3 ± 0.8	8.1 ± 0.7	7.9 ± 0.7	7.6 ± 0.5	7.4 ± 0.6** <sup>#</sup>
Lean mass, kg						
Appendicular	22.2 ± 4.9	22.4 ± 4.7	22.7 ± 3.9	22.3 ± 3.5	18.6 ± 4.5	18.0 ± 4.6**††
Lower limbs	16.9 ± 3.4	17.2 ± 3.3*	17.7 ± 3.5	17.7 ± 3.0	14.2 ± 3.2	13.9 ± 3.4††
Upper limbs	5.4 ± 1.6	5.3 ± 1.5	5.8 ± 1.1	5.1 ± 1.4**	4.4 ± 1.3	4.1 ± 1.3** <sup>#†</sup>
Fat mass, kg						
Appendicular	11.9 ± 3.8	12.1 ± 3.9**	10.2 ± 3.2	9.2 ± 3.2** <sup>#</sup>	10.0 ± 4.1	9.1 ± 4.4** <sup>#</sup>
Lower limbs	9.1 ± 2.9	9.8 ± 3.4	8.7 ± 2.7	7.6 ± 2.8* <sup>†</sup>	7.8 ± 2.9	7.6 ± 3.6**
Upper limbs	2.4 ± 0.8	2.5 ± 0.8	2.4 ± 0.8	1.9 ± 0.5*	2.3 ± 1.0	2.0 ± 1.3** <sup>†</sup>

FFMI, fat-free mass index.

\**P* < 0.05.\*\**P* < 0.01.\*\*\**P* < 0.001 vs. baseline.<sup>#</sup>*P* < 0.05.<sup>†</sup>*P* < 0.01 vs. weight gain/stable weight group.††*P* < 0.05.†††*P* < 0.001 vs. moderate weight loss group.**Figure 2** (A) Assessment of functional capacity according to the Barthel Index in study subgroups. (B) Assessment of degree of disability according to the modified Rankin Scale in study subgroups. (C) Relationship between the functional outcome and weight change at 12 months follow-up

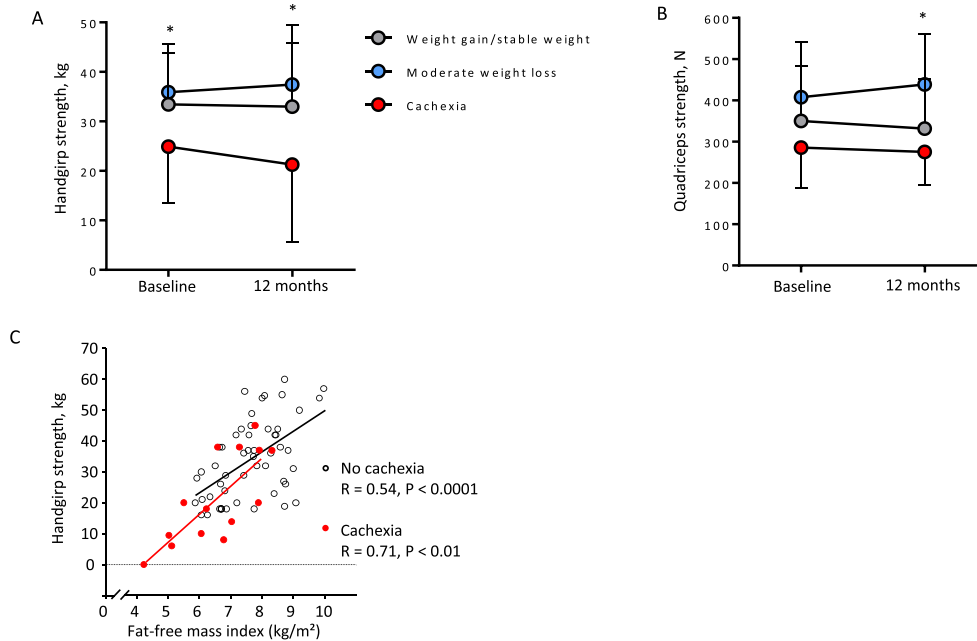
pulmonary disease has been shown previously.<sup>25,37</sup> In the present study, cachectic patients showed similar signs of inflammatory activation with elevated CRP levels assessed at 12 months follow-up accompanied by lean tissue depletion, low functional capacity, and reduction of body weight. A relation between systemic inflammation and loss of muscle strength and muscle thickness in population-based clinical trials has been reported previously.<sup>27,38</sup> In experimental setting, administration of the inflammatory markers in rats caused

muscle protein breakdown.<sup>39</sup> Thus, our results were in accordance with previous observations.

Our recent studies investigating cachexia in patients with chronic heart failure suggested an association of cardiac cachexia with gastrointestinal congestion, increased concentration of gut bacteria, and systemic inflammation.<sup>37,40</sup> Further, changes in gut microbiota after stroke were linked to increased pro-inflammatory cytokines levels.<sup>41</sup> Several pathways linking systemic inflammation to the brain and



**Figure 3** (A) Maximal handgrip strength in study subgroups. (B) Maximal quadriceps strength in study subgroups. (C) Association of fat-free mass index with maximal handgrip strength in patients with and without cachexia at 12 months follow-up



**Table 4.** Risk factors associated with functional dependency defined by Barthel Index <60 at 12 months follow-up

Parameter	OR	95% CI	P-value
Lean tissue wasting	44.8	[4.17–481.56]	0.002
Presence of cachexia	20.8	[2.09–206.15]	<0.01
Undernourished/at risk for malnutrition	14.7	[0.99–215.37]	0.05
Body mass index <25 kg/m <sup>2</sup>	11.5	[1.19–110.67]	0.04
C-reactive protein, log[mg/L]	10.1	[1.39–73.54]	0.02
NIHSS, point	1.43	[1.07–1.90]	0.02
Delta weight loss, kg	0.82	[0.68–0.99]	0.04
Body mass index, kg/m <sup>2</sup>	0.68	[0.50–0.93]	0.02
MNA scale, point	0.57	[0.37–0.87]	0.01
Albumin, g/L	0.75	[0.60–0.94]	0.01
FFMI, kg/m <sup>2</sup>	0.16	[0.04–0.63]	0.01
Lean mass arms, kg	0.24	[0.06–0.92]	0.04
Lean mass legs, kg	0.58	[0.38–0.89]	0.01
Appendicular lean mass, kg	0.66	[0.47–0.93]	0.02
Handgrip strength, kg	0.89	[0.81–0.99]	0.04
Multivariable logistic model adjusted for age and sex			
I. Lean tissue wasting	137.9	[2.04–9324.7]	0.02
II. FFMI, kg/m <sup>2</sup>	0.11	[0.13–0.99]	<0.05

FFMI, fat-free mass index; NIHSS, National Institute of Health Stroke Scale; MNA, Mini Nutritional Assessment.

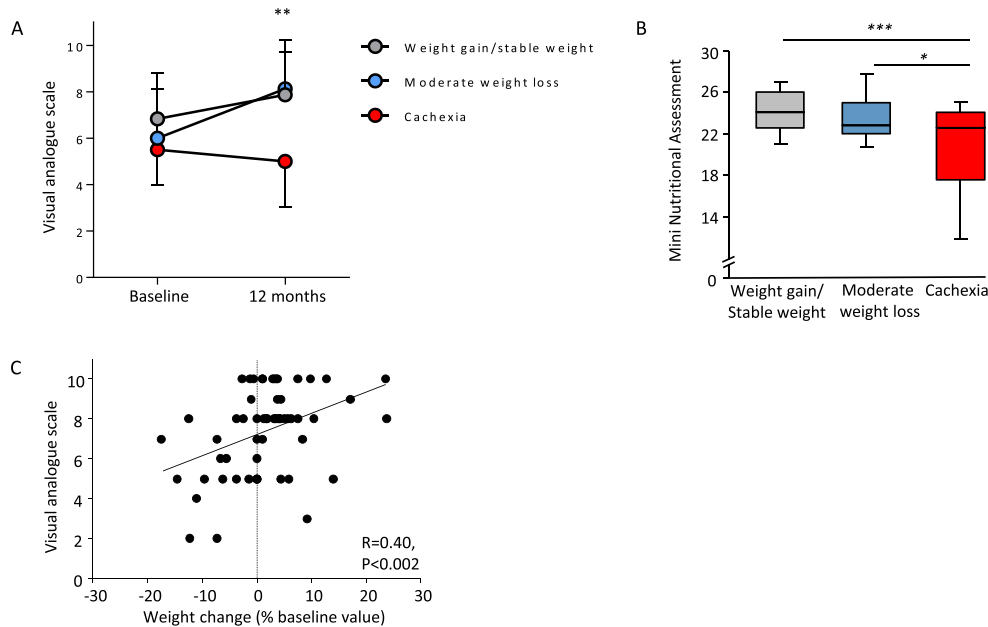
responsible for development of ‘sickness behaviour’ with attenuated parasympathetic tone, reduced appetite, altered thermoregulation, and impaired energy metabolism were previously described.<sup>42</sup> Accordingly, we observed an association between systemic inflammation and reduced nutritional status in patients with stroke. Cachectic patients had the lowest appetite leading to decreased food intake. An involvement of anorexia in regulation of body composition in chronic inflammatory disease and cachexia development was suggested.<sup>25</sup> Therefore, ongoing systemic

inflammation in chronic stroke might lead to increased metabolic drive, appetite loss, and energetic deficit resulting in proteolytic breakdown and tissue wasting.<sup>25,43</sup>

## Functional limitations

In the present study, we showed implications of cachexia on functional outcome after stroke. Cachectic patients had the

**Figure 4** (A) Self-reported appetite score according to visual analogue scale in study subgroups. (B) Nutritional status according to Mini Nutritional Assessment score in patient subgroups at 12 months follow-up. (C) Association of body weight change with score by visual analogue scale at 12 months follow-up



**Table 5.** Risk factors associated with the presence of systemic inflammation at 12 months follow-up serving as dependent variable

Parameter	OR	95% CI	P-value
Lean tissue wasting	5.20	[0.99–27.09]	0.05
Changes of body weight, kg	0.89	[0.80–1.01]	0.06
Appetite according to VAS, point	0.71	[0.52–0.97]	0.03
Undernourished/at risk for malnutrition	0.81	[0.69–0.99]	0.04
Modified Rankin Scale, point	1.96	[1.16–3.31]	0.01
Barthel Index, 10 points	0.68	[0.49–0.95]	0.02
Handgrip strength, kg	0.94	[0.89–0.99]	0.02

VAS, visual analogue scale.

most severe stroke-related disability across the study groups as assessed by the BI and mRS, although they significantly improved their functional status at 12 months follow-up. We showed that the presence of cachexia and the lean tissue depletion were associated with the low functional capacity as defined by the BI.<sup>23</sup> Further, both lower BMI and higher body weight loss were more frequently observed in patients with higher degree of functional dependence. Therefore, our findings are in accordance with the previous clinical trials, investigating cachexia in chronic diseases and suggesting its unfavourable impact on activities of daily living, clinical and functional outcome.<sup>25,37</sup>

Additionally, to the BI and mRS, the study protocol considered a performance of the short physical performance battery (SPPB).<sup>22</sup> SPPB is widely used in geriatric medicine and includes examination of standing ability, time walking of 3 or 4 m, and time to rise from the chair.<sup>44</sup> It became apparent

in the study that the SPPB was less suitable to evaluate the functional capacity due to coordination deficit if patient had a paretic limb. Hence, merely 51% of all patients (i.e. 21% of the cachectic group) at baseline and 82% of the patients (57% of the cachectic group) at 12 months follow-up were able to complete the SPPB, which indicates a relevant floor effect as discussed previously.<sup>12</sup> We performed a 4 m of gait test as a part of the SPPB during the baseline and 12 months follow-up. The gait speed at baseline was  $1.1 \pm 0.3$  vs.  $0.9 \pm 0.2$  vs.  $0.8 \pm 0.4$  m/s,  $P = 0.3$  in the stable weight vs. moderate weight loss vs. cachectic subgroup, respectively. Twelve months after stroke, gait speed remained identical in all three groups due to the high frequency of paresis in these patients. Thus, due to the relevant floor effect of the test battery in the setting of stroke as well as limited insight into the functional capacity of the patients, we decided to omit these data.



## Weight gain

The majority of patients in the present study increased the weight and improved their functional capacity during the first year after stroke. We observed a correlation between increasing weight and better functional outcome with higher BI, indicating a positive effect of ‘obesity paradox’.<sup>6</sup>

## Limitations

Our study has several limitations. First, the number of patients with stroke is limited. Second, only study patients with mild to moderate stroke deficit were included, thus our results are not generalizable to patients with severe stroke. Therefore, further longitudinal studies are warranted to confirm and extend our findings.

## Conclusions

The observed incidence of cachexia was 21% among the patients with stroke at 12 months follow-up. Overall, more fragile patients defined by higher age, advanced neurological deficit, and functional disability were at risk for cachexia. At 12 months follow-up, cachectic patients remained with the lowest functional and physical status. Development of cachexia after stroke should be recognized as a relevant complication. Better understanding of the interaction between stroke-related brain injury and systemic metabolism seems to be required for better prevention of cachexia in patients with stroke.

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## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1:** Clinical characteristics of patient subgroups at 12 months follow-up

## Conflict of Interest

None declared.

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